PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PRD2076f-PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/051048	International filing date *(day/month/year)* 07 June 2004 (07.06.2004)	Priority date *(day/month/year)* 10 June 2003 (10.06.2003)]
International Patent Classification (IPC) or national classification and IPC [7] A61K 31/33, 31/496, 31/485, 31/4468, A61P 25/00, 25/02, 25/04, 11/00, 1/08, A61K 31/433, A61P 25/36		
Applicant JANSSEN PHARMACEUTICA N.V.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 13 December 2005 (13.12.2005)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Agnes Wittmann-Regis
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: 23/12

see form PCT/ISA/220 AL

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/051048	International filing date *(day/month/year)* 07.06.2004
Priority date *(day/month/year)* 10.06.2003	
International Patent Classification (IPC) or both national classification and IPC A61K31/33, A61K31/496, A61K31/485, A61K31/4468, A61P25/00, A61P25/02, A61P25/04, A61P11/00, A61P1/08,	
Applicant JANSSEN PHARMACEUTICA N.V.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6, 10, 12-13
	No:	Claims	1-5, 7-9, 11, 14-17
Inventive step (IS)	Yes:	Claims	6
	No:	Claims	1-5, 7-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Re Item V : Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.2.1.
The Applicant's attention is drawn to the fact that claim 1 is not clear to the International Searching Authority (Article 6 PCT). Indeed, it is considered to be directed to a NK-1 antagonist pharmaceutical composition and its use to treat pain and side-effects associated with opioids. This claimed subject-matter is supported by the description on page 17, lines 1-6, which states that the NK-1 antagonist may be formulated in a single pharmaceutical product and in claim 7, which claims the separate, sequential or simultaneous use of the NK-1 antagonist with an opioid. Further, claims 16-17 are also directed to the use of a NK1 antagonist alone for the treatment of pain and side-effects associated with opioids. It does not seem therefore that claim 1 is exclusively directed to a combination of a NK-1 antagonist with an opioid. Thus, a patient being treated with opioids for the treatment of pain and additionally receiving a pharmaceutical composition containing a NK-1 antagonist, which will reduce the side-effects of the opioid, will be novelty destroying for claim 1. Now the subject-matter of independent claims 16 and 17 is already known. Indeed, the use of a NK-1 antagonist for the treatment/prevention of emesis, tolerance, respiratory depression and other side-effects induced by opioids is known in the prior art. Similalry, the use of a NK-1 antagonist combined with an opioid analgesic to treat pain (the combination bringing an additive effect) is also known in the prior art (see item V.2.2 below). Claim 1 is therefore not considered new in view of this prior art.

The Applicant's attention is also drawn to the fact that since claims 16-17 are not new, the requisite unity of invention (Rule 13.1 PCT), therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of dependent claims. As they stand the wordings of the present claims do not therefore meet the requisite of unity of invention (Rule 13.1 PCT). The unity objection has however not been raised in the International Search Report, since a simple rewording of the subject-matter to be claimed could easily overcome the objection.

V.2.2.
Reference is made to the following documents :

D1 : US-B-6 197 7721
D2 : US-A-5 880 132
D3 : GB-A-2 287 404

Unless otherwise stated, reference is made to the relevant passages cited in the International Search Report for each of these documents.

D1 describes piperidinyl-piperazine derivatives, some of which being the same as the ones of the present application, as NK1-receptor antagonists and their use in the treatment of chronic neuropathic pain and emesis induced by opioids such as morphine. Thus, and under the provision of item V.2.1. above, claims 1-5, 7-9, 11 and 14-15 are not considered new in view of D1 (Article 33(2) PCT).

D2 describes the use of a NK1-receptor antagonist associated with an opioid analgesic compound for the treatment of pain and chronic neuropathic pain. Thanks to this combination, the respiratory depression, constipation, nausea, vomiting, tolerance, dependence and problems of drug withdrawal associated with opioid drugs are also prevented and/or treated. D2 Further states that the combination presents an additive analgesic effect. The compounds of D2 are different from the ones of the present application, thus, only claims 16-17 are not new in view of D2 (Article 33(2) PCT).

D3 describes the combination of a NK1-receptor antagonist with a narcotic analgesic compound (such as codeine, fentanyl, sufentanyl and morphine) and their use to treat acute and chronic pain. In D3, no particular NK-1 antagonist is disclosed, therefore claims 1-17 appear new in view of this document (Article 33(2) PCT).

Accordingly, claims 6, 10 and 12-13 appear new in view of D1-D3 (Article 33(2) PCT).

From these remaining claims, only claim 6 appears to involve an inventive step, since the specific NK-1 antagonists of said claim were neither disclosed not suggested in the prior art (Article 33(3) PCT).

V.2.3. Clarity objection :

Claim 6, by reference to chemical compound numbers, does not meet the requirements of Article 6 PCT and Rule 6.2(a) PCT.

Re Item VI : Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/033428 A	22.04.2004	07.10.2003	08.10.2002

D4 (WO 2004/033428 A) describes the piperazine derivatives of the present application, as NK-1 antagonists, and their use to treat postoperative pain, but also emesis and tolerance induced by opioids.